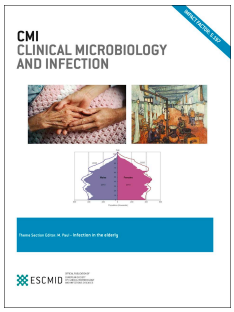
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal Pre-proof



Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: A systematic review and meta-analysis

Mohamad Salim Alkodaymi, MBBS, MPH, Osama Ali Omrani, MBBS, BSc, Nader A. Fawzy, Bader Abou Shaar, Raghed Almamlouk, MBBS, Muhammad Riaz, PhD, Mustafa Obeidat, MBBS, MBA, Yasin Obeidat, MBBS, Dana Gerberi, MLS, Rand M. Taha, Zakaria Kashour, MBBS, Tarek Kashour, MBChB, Elie F. Berbari, MD, Khaled Alkattan, MD, Imad M. Tleyjeh, MD, MSc

PII: S1198-743X(22)00038-6

DOI: https://doi.org/10.1016/j.cmi.2022.01.014

Reference: CMI 2808

To appear in: *Clinical Microbiology and Infection*

Received Date: 2 July 2021

Revised Date: 13 January 2022

Accepted Date: 17 January 2022

Please cite this article as: Alkodaymi, MS, Omrani, OA, Fawzy NA, Shaar BA, Almamlouk, R, Riaz, M, Obeidat, M, Obeidat, Y, Gerberi, D, Taha RM, Kashour, Z, Kashour, T, Berbari, EF, Alkattan, K, Tleyjeh, IM, Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: A systematic review and meta-analysis, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.01.014.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Journal Pre-proof

Prevalence of Post-acute COVID-19 Syndrome Symptoms at Different Follow-up Periods: A Systematic Review and Meta-Analysis

Running title: PACS Symptoms at Different Follow-up Periods

Authors:

1. Mohamad Salim Alkodaymi[1], MBBS, MPH*
2. Osama Ali Omrani[2,3], MBBS, BSc*
3. Nader A. Fawzy[4#]
4. Bader Abou Shaar[4#]
5. Raghed Almamlouk[4], MBBS[#]
6. Muhammad Riaz[5], PhD[#]
7. Mustafa Obeidat[4], MBBS, MBA
8. Yasin Obeidat[6], MBBS
9. Dana Gerberi[7], MLS
10. Rand M. Taha[4]
11. Zakaria Kashour[4], MBBS
12. Tarek Kashour[8], MBChB
13. Elie F. Berbari[9], MD
14. Khaled Alkattan[4], MD
15. Imad M. Tleyjeh[4,9,10,11], MD, MSc

* These 2 authors contributed equally as first authors

[#] These 4 authors contributed equally as second authors

1. Department of Family & Community Medicine, Alfaisal University, Riyadh, Saudi Arabia
2. The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom.
3. Barts and the London School of Medicine and Dentistry, Queen Mary University, London, United Kingdom

Journal Pre-proof

4. College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
5. Center for Clinical Trial Research, School of Medicine, Cardiff University, United Kingdom
6. UMass chan medical school, Baystate, MA, USA
7. Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, USA
8. Department of Cardiac Sciences, King Fahad Cardiac Center, King Saud University Medical City, Riyadh Saudi Arabia
9. Infectious Diseases Section, Department of Medical Specialties King Fahad Medical City, Riyadh, Saudi Arabia
10. Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
11. Department of Epidemiology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA

Corresponding Author:

Imad M. Tleyjeh, MD, MSc, FACP, FIDSA

Professor of Medicine and Epidemiology

Section of Infectious Diseases, King Fahd Medical City

PO Box 59046, Riyadh 11525, Saudi Arabia

Phone: 00966112889999

Tleyjeh.Imad@mayo.edu

Abstract word count: 336

Paper word count: 3518

Journal Pre-proof

Journal Pre-proof

Abstract

Background: Post-acute COVID-19 Syndrome is now recognized as a complex systemic disease that is associated with substantial morbidity.

Objectives: To estimate the prevalence of persistent symptoms and signs at least 12 weeks after acute COVID-19 at different follow-up periods.

Data sources: Searches were conducted up to October 2021 in Ovid Embase, Ovid Medline, and PubMed.

Study eligibility criteria: Articles in English that reported the prevalence of persistent symptoms among individuals with confirmed SARS-CoV-2 infection and included at least 50 patients with a follow-up of at least 12 weeks after acute illness.

Methods: Random-effect meta-analysis was performed to produce pooled prevalence for each symptom at 4 different follow-up time intervals. Between-studies heterogeneity was evaluated using the I^2 statistic and was explored via meta-regression, considering several a priori study level variables. Risk of bias was assessed using the Joanna Briggs Institute (JBI) tool and the Newcastle-Ottawa Scale for prevalence studies and comparative studies, respectively.

Results: After screening 3209 studies, a total of 63 studies were eligible, with a total COVID-19 population of 257,348. The most commonly reported symptoms were fatigue, dyspnea, sleep disorder and concentration difficulty (32%, 25%, 24%, and 22% respectively at 3-<6 months follow-up), effort intolerance, fatigue, sleep disorder and dyspnea (45%, 36%, 29% and 25% respectively at 6-<9 months follow-up), fatigue (37%) and dyspnea (21%) at 9-<12 months and fatigue, dyspnea, sleep disorder, myalgia (41%, 31%, 30%, and 22% respectively at >12 months follow-up). There was substantial between-studies heterogeneity for all reported symptoms prevalence. Meta-regressions identified statistically significant effect modifiers: world region, male gender, diabetes mellitus, disease severity and overall study quality score. Five of six studies including a comparator group consisting of COVID-19 negative cases observed significant adjusted associations between COVID-19 and several long-term symptoms.

Conclusions: This systematic review found that a large proportion of patients experience PACS 3 to 12 months after recovery from the acute phase of COVD-19. However, available studies of PACS are highly heterogeneous. Future studies need to have appropriate comparator groups, standardized symptoms definitions and measurements and longer follow-up.

Journal Pre-proof

INTRODUCTION

A significant number of patients who have recovered from acute COVID-19 infection are reporting lasting symptoms resulting in impairment of everyday activities beyond the initial acute period. These post COVID-19 patients suffer from a phenomenon known as "long" or "chronic" COVID-19 or more recently, Post-Acute Sequelae of COVID-19 or Post-Acute COVID-19 syndrome (PACS) (1,2).

The terms "long COVID-19" and "post-acute COVID-19 syndrome (PACS)" lack a unified definition. The definition endorsed by the National Institute for Health and Care Excellence (NICE) and the World Health Organization (WHO) as a set of “signs and symptoms that emerge during or after an infection consistent with COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis” (3,4). Many experts including the NICE panel also agree to subdivide into two categories: 1- post-COVID-19 subacute phase of ongoing symptoms that last 4-12 weeks after the onset of illness, and 2- chronic phase or long COVID-19, defined as symptoms and abnormalities that last more than 12 weeks after the onset of illness and are not explained by an alternative diagnosis (2,4).

This timeframe distinction is important because it differentiates between the acute illness and the sequelae of possibly an irreversible tissue damage with varying degrees of dysfunction and symptoms potentially involving several possible conditions as suggested by some experts: post-intensive care syndrome, post-thrombotic or hemorrhagic complications, acute-phase immune-mediated complications, and/or multi-systemic inflammatory syndrome in children or adults (5). Globally, the number of patients recovering from COVID-19 infection continues to grow at an unprecedented rate. Therefore, we sought to perform a systematic review and meta-analysis of available literature to

estimate the prevalence of persistent symptoms and signs after at least 12 weeks of acute COVID-19 at different follow-up (FU) periods.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for study design, search protocol, screening, and reporting (6,7).

Literature Search and Studies Selection

The literature was searched by a medical librarian for the concepts of long-term symptoms in patients infected by Covid-19. Search strategies were created using a combination of keywords and standardized index terms. Searches were originally run in November 2020 and updated in January and September 2021 in Ovid Embase, Ovid Medline (including publication ahead of print, in-process & other non-indexed citations) and PubMed.gov which includes preprints. Results were limited to English language and primarily adult studies. All citations were exported to EndNote where 4,539 duplicates were removed leaving 3,921 citations. Search strategies are provided in the supplementary material (Supplement 1).

Articles were considered eligible for inclusion if they (1) were written in the English language; (2) were peer-reviewed cohort, case-control or cross-sectional studies that reported the prevalence of persistent symptoms among individuals with SARS-CoV-2 infection; (3) included at least 50 patients (4) had follow-up of at least 3 months after symptoms onset (as per the NICE definition), (5) all patients with laboratory confirmed COVID-19 and (6) follow-up reported as mean, median or set-interval following symptoms onset, diagnosis, acute illness or initial CT chest imaging. Where studies had overlapping investigated populations, studies with larger sample sizes were prioritized with the remainder excluded (8).

We subsequently identified a subgroup of these eligible studies that included studies with a comparator group consisting of non-COVID cases.

Identification of Studies

Six reviewers (O.O., M.S.A., M.O., N.A.F., R.A., B.A.S.) examined the titles and abstracts of articles in pairs, using the above pre-defined selection criteria. This was followed by a full text review of each article to confirm meeting the eligibility criteria. Disagreements regarding inclusion of a full-text article were discussed and agreed with the senior reviewer (IT).

Data Collection

Data were extracted simultaneously by six reviewers in duplicates (OO, NAF, BAS, RA, MSA, MO) into a pre-specified data collection form, with any discrepancies resolved in consultation with the senior reviewer (IMT). Data were collected across the following domains: study characteristics, follow-up method, baseline demographics and symptom prevalence. Full details of the data collation variables can be found in the supplementary material (Supplement 2).

Quality Assessment

The reviewers independently assessed the risk of bias for each study using the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies. JBI critical appraisal checklist for studies reporting prevalence consists of nine questions: (1) Sample frame suitability,(2) Sampling method appropriateness (3) Sample size adequacy,(4) Proper description of study subjects and setting, (5) Sufficient coverage of the identified sample (6) Usage of valid methods for identification of the condition, (7) Standard and reliable way of measurement of the condition for all participants, (8) Appropriate statistical analysis and (9) Adequate response rate (9). Each study was assessed across each of these questions and determined as either 'Yes', 'No' or 'Unclear'. Studies were assigned an overall score, reflecting the number of questions with a ‘Yes’ response.

Studies with a comparator group consisting of non-COVID cases were assessed using the Newcastle-Ottawa Scale (NOS) (10).The NOS rates observational studies based on 3 parameters: selection, comparability between exposed and unexposed groups, and exposure and outcome assessment. These 3 domains can have a maximum score of 4, 2, and 3 stars, respectively. Studies with <5 stars are considered low quality, 5–7 stars moderate quality, and >7 stars high quality.

Data Synthesis

Our outcome of interest was prevalence of symptoms at follow-up across four different follow up intervals: 3-<6 months, 6-<9 months, 9-<12 months and ≥12 months. Due to varying definitions of "day 0" to follow up across the literature, we accepted definitions of "day 0" that include COVID-19 symptom onset, COVID-19 diagnosis or hospital discharge after acute illness. We further categorized studies according to the severity of COVID-19, which was defined in this context as patients' setting during acute illness: ranging from outpatient (OP), general inpatient wards (IP) or intensive care unit (ICU) settings. Where symptoms prevalence at follow-up was not reported separately based on COVID-19 severity, studies were described as "mixed", for example "mixed IP/ICU".

The range of persistent COVID-19 symptoms reported to date was then identified and categorized. Given the exchangeable terminology to refer to symptoms across studies, the following terms were grouped: "sleep disturbance" to refer to insomnia, daytime sleepiness, sleep difficulties, and/or sleep disorders, "concentration difficulties" to refer to confusion, change in level of consciousness and/or concentration, "cognitive impairment" to refer to cognitive dysfunction, brain fog, and/or cognition difficulties, "loss of taste" to refer to taste dysfunction, alteration of taste, dysgeusia, and parageusia, "loss of smell" to refer to smell dysfunction, alteration of smell, anosmia, hyposmia, smell blindness, and olfactory disorders. Signs and symptoms were divided into 7 main systems: mental health, respiratory

system, cardiovascular system, musculoskeletal system, nervous system, gastrointestinal system and other.

Statistical Analyses

The total cohort number and the number of patients with different symptoms or complaints were extracted from each study at different follow up times into 4 intervals: 3-<6 months, 6-<9 months, 9-<12 months and ≥12 months. We performed separate meta-analyses for the aforementioned follow up intervals where ≥3 studies reported symptom prevalence at that follow up interval. The arcsine transformation was used to obtain a pooled estimate of the prevalence of each symptom. As conventional meta-analysis models assume normally distributed data, the arcsine-based transformations are applied to the proportion data to yield better approximations to the normal distribution and they have the important advantage of stabilizing variances (11,12). We used DerSimonian and Laird random effect model with inverse variance method to pool prevalence (13). We performed subgroup meta-analyses by severity of acute COVID-19 in the included studies, thereby allowing a visual display of heterogeneity due the differences in the severity of illness in reporting studies. We evaluated between-studies heterogeneity using the I^2 statistic, which estimates the variability percentage in effect estimates that is due to heterogeneity rather than to chance (14). Two-tailed $p<0.05$ were considered statistically significant.

We performed meta-regression to explore between studies heterogeneity. We considered several a priori chosen study level variables based on clinical plausibility (Supplement 3). Meta-regression was performed for each symptom where ≥10 studies reported prevalence at any given follow-up interval as per the Cochrane Handbook for Systematic Reviews (15).The regression coefficients obtained from the meta-regression analyses describe how the outcome variable (the pooled prevalence) changes with a unit increase in the continuous explanatory variable and changes for the category of interest compared

to a reference category for a categorical variable. The statistical significance was considered as p<0.01for the results of the meta-regression and we reported if a variable was found to be a significant contributor to heterogeneity. All statistical analyses were performed using Stata 12 statistical software StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. (16).

RESULTS

Of the 3209 abstracts screened, 152 full-text articles were reviewed with 63 included in the final analysis (Figure 1) (17–79). After full article review, the most common reason for exclusion was the absence of reported data on symptom prevalence at stated follow-up (n=36), followed by the inclusion of COVID-19 patients without laboratory confirmed COVID-19 (n=23). Of the 63 included studies (total COVID-19 population = 257348), six were from North America (COVID-19 sample size = 237261), twelve from East Asia (COVID-19 sample size = 10162), thirty-seven from Europe (COVID-19 sample size = 8998) and eight from North Africa, the Middle East, or South Asia (COVID-19 sample size = 927) (Table 1). The majority of included studies were single center (n = 43), followed by multicenter (n = 18) with two nationwide studies. Only four studies included follow up equal to or greater than 365 days (sample size = 1246), with five studies with follow up of 270 to 364 days (sample size = 3758), twenty-five studies with follow up of 180 to 269 days (sample size = 243576) and the majority of studies with follow up of 90 to 179 days (n = 33, sample size = 9323).

Meta-analyses of prevalence of symptoms at different follow up periods

Meta-analysis highlighted the substantial heterogeneity between symptom prevalence's reported across studies, with I^2 statistics ranging from 75.4% (difficulty concentrating at 3-<6 months follow up) to 99.4% (fatigue at 9-<12 months follow up), with the vast majority of symptoms across all follow up intervals producing an $I^2 \geq 90\%$. The most commonly reported symptoms between 3-<6 months are fatigue (32%,

95% CI = 22-44%, number of studies = 25, sample size = 7268) followed by dyspnea (25%, 95% CI = 17-34%, number of studies = 28, sample size = 8132), sleep disorder (24%, 95% CI = 8-44%, number of studies = 8, sample size = 4369) and concentration difficulty (22%, 95% CI = 15-31%, number of studies = 5, sample size, = 466). Between 6-<9 months, the most common symptoms reported were effort intolerance (45%, 95% CI – 25-67%, number of studies = 5, sample size = 850), fatigue (36%, 95% CI = 27-46%, number of studies = 19, sample size 8191), sleep disorder (29%, 95% CI 15-45%, number of studies = 12, sample size = 242000), and dyspnea (25%, 95% CI = 20-30%, number of studies = 13, 4384). In the 9-<12 months period, the meta-analysis included 9 symptoms with the highest prevalence reported for fatigue (37%, 95% CI = 16-62%, number of studies = 5, sample size = 3758) and dyspnea (21%, 95% CI = 14-28%, number of studies = 5, sample size = 3758), with loss of taste being the least reported (6%, 95% CI 1-13%, number of studies = 3, sample size = 1742). Similarly, fatigue was the most reported symptom (41%, 95% CI 30-53%, number of studies = 4, sample size = 1246) in the >12 months period. It is noteworthy that fatigue, dyspnea, myalgia, and sleep disorder were most reported in the >12 months interval; while cough, headache, loss of taste and loss of smell were most common at 6-<9 months (Figure 2, Panels A-B, Supplement 6, Panels C-D).

Exploring Heterogeneity

Due to a limited number of studies reporting symptom prevalence at 9-<12 months or ≥12 months, meta-regression was performed for symptom prevalence at 3-<6 months and 6-<9 months (Supplement 6). Observed statistically significant effect modifiers included: world region where the study was conducted, percentage of study participants who were men, and those who had DM, disease severity category as defined earlier and the overall study quality score.

Studies reporting results from Asian populations reported a lower prevalence of fatigue, dyspnea, loss of smell and loss of taste at 3-6 month follow up and a lower prevalence of fatigue at 6-9 month follow up.

A higher proportion of men was found to be associated with a lower prevalence of cough and loss of smell at 6-9 months follow up, whilst a higher proportion of diabetes mellitus as a comorbidity was associated with a lower prevalence of loss of smell and taste at 3-6 and 6-9 month follow up. Studies investigating patients in ICU were associated with a higher prevalence of dyspnea compared to studies investigating an OP population at 3-6 month and 6-9 month follow up intervals. Higher study quality was found to be associated with lower prevalence of dyspnea at 3-6 months and cough at 6-9 months follow up.

Studies with a COVID-19 negative comparator group

A total of 6 studies reporting symptoms prevalence included a comparator group consisting of COVID-19 negative cases, with a summary of their findings presented in Table 2 (17,24,26,37,59,62). Of these, 2 studies compared long term symptom prevalence of COVID-19 cases to either influenza, pneumonia or other respiratory tract infection cases (17,26). Overall, all but one study reported higher prevalence of symptoms or adverse event in cases following COVID-19 compared to respective comparator groups, with one negative study specifically assessing olfactory and gustatory dysfunction at 6 months (37). Two out of 6 studies were rigorously designed. One study observed that COVID-19 cases had significantly higher hazard of mood disorder, anxiety and insomnia when compared to matched cohorts with influenza or respiratory tract infection (26). Another study observed that COVID-19 cases have significantly higher prevalence of symptoms at 6 and 9 months follow-up when compared to community controls, including fatigue, sleep difficulties, hair loss, smell disorder, taste disorder, palpitations, chest pain and headaches (45).

Quality Assessment

Studies without comparator groups

Journal Pre-proof

The studies were generally assessed to have good quality with a mean average critical appraisal score across all studies of 7.97/9. The question that affected the scores the most was "Was the sample size adequate?", with few studies demonstrating appropriate sample size calculations nor representing a significantly large enough sample to provide high external validity (Table S1).

Studies with comparator groups

Study quality was assessed via the NOS as moderate to high, ranging from 5 to 9 (maximum 9), with a number of studies using an non-representative sample of healthcare workers (37,59), or having comparability concerns by not adequately matching cases with the comparator group (17,37,59,62) (Table S2).

DISCUSSION

Summary of the findings

In this systematic review and meta-analysis of 63 studies with a total of 257,348 COVID-19 patients from different world regions, we observed that patients report several clinically significant symptoms across many organs systems 3 months post-acute COVID-19. In addition, we observed that the high between-studies heterogeneity of reported symptoms prevalence could at least be partially explained by clinically plausible effect modifiers such as acute COVID-19 severity, and certain patients' demographics and comorbidities (26,45,80,81).

Our findings lend more support to the initiatives of several countries and organizations that have started to fund more research and disseminate guidelines to better understand, diagnose and treat PACS (8,82,83).

Mechanisms

It remains unknown what proportion of these lingering symptoms are true sequalae of COVID-19 vs. the effects of underlying chronic diseases or pandemic effects on individuals and societies (84,85). Although most studies did not have a control group, the association of certain symptoms with COVID-19 infection among the 6 studies that had appropriate comparator groups supports our findings of a significant burden of PACS. Recent rigorously conducted comparative studies that examined the risk of new clinical sequalae rather than persistent symptoms at 6-month follow-up have shown a higher risk of long-term complications and incident diagnoses after acute COVID-19 infection, among non-hospitalized cases when compared to a matched non-COVID cohort, and hospitalized COVID-19 cases when compared to matched hospitalized influenza cases or when compared to other non-COVID viral lower respiratory tract illnesses. An increasing risk gradient of new sequalae was observed with increasing COVID-19 severity (86,87).

Nevertheless, the mechanisms that explain these chronic symptoms after COVID-19 are not yet fully understood. In addition to the direct effects of SARS-CoV-2, the immune response to the virus is believed to be partly responsible for the appearance of these lasting symptoms, possibly through facilitating an ongoing hyperinflammatory process (88). Several hypotheses have been proposed to explain the long-term outcomes of COVID-19 infection: a) Sequalae of COVID-19 organ involvement during acute infection, b) COVID-19 patients with chronic symptoms may harbor the virus in several potential tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs, c) cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity, d) delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue repair, e) mitochondrial dysfunction and impaired immunometabolism, and f) alterations in microbiome leading to long-term health consequences of COVID-19 (88–91).

Journal Pre-proof

Comparison to other studies

Our systematic review provides a rigorous and unique update of previous attempts by other investigators. First, a number of previous reviews either did not assess the included studies for risk of bias or utilized an inappropriate assessment tool, such as the Newcastle-Ottawa Scale for non-comparative studies. We observed that the quality of included studies to be a significant contributor to heterogeneity of reported symptoms prevalence, with lower quality studies reporting higher prevalence of certain symptoms (92,93). Second, other systematic reviews have included studies with short follow-up periods between one and three months after acute illness and hence do not provide an indication of persistent and chronic symptoms that are defined beyond 12 weeks as per NICE (92–95). Third, although previous studies have performed meta-analysis, with Michelen et al. performing meta-regression for variables of ICU admission and proportion female and Iqbal et al. performing thorough sub-group analysis, no previous systematic review has separated symptoms prevalence across different follow-up intervals or considered other important effect-modifiers for meta-regression (96,97). Finally, and importantly, we present the first attempt to identify and assess studies including an appropriate non-COVID group to provide additional evidence of the association between COVID-19 and the high prevalence of symptoms at follow-up.

Although our review included the most recent eligible studies with the largest sample size, there is a degree of consistency between the findings of symptoms prevalence between our meta-analyses and others. We report a prevalence of fatigue of 32%, 36%, 47% and 41% across follow up periods from 3 to 6 months, 6 to 9 months, 9 to 12 months and greater than 12 months respectively, which is comparable to the findings of Michelen et al. (30.1%) and Iqbal et al. (37%). This similarity is also the case for dyspnea, with previous meta-analysis reporting estimates of prevalence between 25 and 35%, as well as myalgia and hair loss.

330

331 **Strengths and Limitations**

332 Our study is the largest and most comprehensive systematic review of persistent symptoms after acute
333 COVID-19 to date. However, it has a number of limitations inherent to the included studies and studies
334 design. As noted by previous systematic reviews on this topic, studies included in our review lacked
335 uniform symptom terminology, standardized recording methods, and grouping of multiple symptoms
336 under umbrella terms. This limited our ability to compare prevalence and frequency of these symptoms
337 across the studies. Severity of illness was not described in numerous studies, with results presented for
338 whole cohorts and not presented as sub-groups. Thus, grouping all symptoms of various disease severity
339 yield inaccurate estimates of symptoms frequencies. The high observed statistical heterogeneity as
340 measured by I^2 limit the interpretation of the pooled frequencies, although our extensive meta-
341 regression illuminates significant contributors to this heterogeneity; namely severity as defined by
342 highest level of medical care, geographic location, prevalence of diabetes and method of assessing
343 symptom at follow-up (98).
344 We agree with Nasserie et al. in their recommendations about areas of improvement in future research
345 of PACS whether in the conduct of studies or reporting of the various characteristics of symptoms for
346 such conditions including the use of a standardized definition for symptoms and time-zero and including
347 an objective measure of symptom severity and duration. There is a need for further rigorously
348 conducted cohort studies in order to quantify the relative risk of developing long term symptoms
349 following acute COVID-19 infections in comparison to non-COVID-19 comparator group, including
350 healthy controls and those with other acute respiratory infections (94,97,99).

351

352 **CONCLUSION**

Journal Pre-proof

In this large systematic review, we observed, with high degree between-study heterogeneity, that a large proportion of COVID-19 patients have persisting and varying symptoms for several months after the acute infection. While there remain many unanswered questions about PACS, our study brings more evidence from a large number of patients and across different worldwide populations about the prevalence of the long-term effects of COVID-19. Our data support the recent global efforts to conduct additional research to address its underlying mechanisms, epidemiology, diagnosis, and treatment of PACS.

Conflict of interest statement

The authors declare no conflicts of interest.

EFB : UTD honorarium <5 k Per year and member of advisory board for **DEBIOPHARM INTERNATIONAL S.A.**

Funding

No funding was received for this work.

Authors Contribution:

Authors are listed in alphabetical order. Conceptualization: I.M.T. and T.K.; Supervision: I.M.T. and K.M.T.; Project Administration: M.S.A and O.A.O.; Formal Analysis: M.R.; Data Curation: B.A.S., D.G., M.S.A., M.O., N.A.F., O.A.O., R.A., Y.O., and Z.K.; Visualization: M.R., and R.M.T; Writing – Original Draft: B.A.S., M.S.A., N.A.F., O.A.O., and R.A.; Writing Review & Editing: E.F.B. and I.M.T.

REFERENCES

1. Sandler CX, Wyller VBB, Moss-Morris R, Buchwald D, Crawley E, Hautvast J, et al. Long COVID and Post-infective Fatigue Syndrome: A Review. Open forum infectious diseases. 2021 Sep 9;8(10):ofab440–ofab440.
2. Nalbandian A, Sehgal K, Gupta A, Madhavan M v, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nature Medicine. 2021;27(4):601–15.
3. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. 2021 [cited 2021 Dec 19]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
4. National Institute for Health and Care Excellence (UK). COVID-19 rapid guideline: managing the long - term effects of COVID-19. 2020 [cited 2021 Dec 19]. Available from: https://www.nice.org.uk/guidance/ng188
5. Lledó GM, Sellares J, Brotons C, Sans M, Antón JD, Blanco J, et al. Post-acute COVID-19 syndrome: a new tsunami requiring a universal case definition. Clinical microbiology and infection. 2021 Nov 24;S1198-743X(21)00661-3.
6. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015 Jan 1;4(1):1.
7. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ : British Medical Journal. 2015 Jan 2;349:g7647.
8. Sivan M, Taylor S. NICE guideline on long covid. BMJ. 2020 Dec 23;371:m4938.
9. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. JBI Evidence Implementation. 2015;13(3).
10. Guyatt G, Busse J. Methods Commentary: Risk of Bias in Cohort Studies. [cited 2021 Dec 18]. Available from: https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies
11. Tleyjeh IM, Kashour Z, AlDosary O, Riaz M, Tlayjeh H, Garbati MA, et al. Cardiac Toxicity of Chloroquine or Hydroxychloroquine in Patients With COVID-19: A Systematic Review and Meta-regression Analysis. Mayo Clinic proceedings Innovations, quality & outcomes. 2021 Feb;5(1):137–50.
12. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. Journal of Epidemiology and Community Health. 2013 Nov 1;67(11):974.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177–88.
14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003 Sep 6;327(7414):557–60.

15. Deeks J, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. [cited 2021 Dec 18]. Available from: https://training.cochrane.org/handbook/current/chapter-10
16. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010 Aug 5;36(3):1–48.
17. Elkan M, Dvir A, Zaidenstein R, Keller M, Kagansky D, Hochman C, et al. Patient-Reported Outcome Measures After Hospitalization During the COVID-19 Pandemic: A Survey Among COVID-19 and Non-COVID-19 Patients. International journal of general medicine. 2021 Aug 26;14:4829–36.
18. Zayet S, Zahra H, Royer P-Y, Tipirdamaz C, Mercier J, Gendrin V, et al. Post-COVID-19 Syndrome: Nine Months after SARS-CoV-2 Infection in a Cohort of 354 Patients: Data from the First Wave of COVID-19 in Nord Franche-Comté Hospital, France. Microorganisms. 2021 Aug 12;9(8):1719.
19. Mechi A, Al-Khalidi A, Al-Darraji R, Al-Dujaili MN, Al-Buthabhak K, Alareedh M, et al. Long-term persistent symptoms of COVID-19 infection in patients with diabetes mellitus. International journal of diabetes in developing countries. 2021 Aug 24;1–4.
20. Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, Martín-Toledano M, López-Larramona G, Ruiz-Chicote AM, et al. Long-Term Outcomes of Patients with Coronavirus Disease 2019 at One Year after Hospital Discharge. Journal of clinical medicine. 2021 Jun 30;10(13):2945.
21. Fernández-de-Las-Peñas C, Guijarro C, Plaza-Canteli S, Hernández-Barrera V, Torres-Macho J. Prevalence of Post-COVID-19 Cough One Year After SARS-CoV-2 Infection: A Multicenter Study. Lung. 2021 Jun;199(3):249–53.
22. Lombardo MDM, Foppiani A, Peretti GM, Mangiavini L, Battezzati A, Bertoli S, et al. Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. Open forum infectious diseases. 2021 Jul 16;8(8):ofab384–ofab384.
23. Boscolo-Rizzo P, Guida F, Polesel J, Marcuzzo AV, Capriotti V, D'Alessandro A, et al. Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). International Forum of Allergy & Rhinology. 2021 Dec 1;11(12):1685–8.
24. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747–58.
25. Clavario P, de Marzo V, Lotti R, Barbara C, Porcile A, Russo C, et al. Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. International journal of cardiology. 2021 Oct 1;340:113–8.
26. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The lancet Psychiatry. 2021 May;8(5):416–27.
27. Menges D, Ballouz T, Anagnostopoulos A, Aschmann HE, Domenghino A, Fehr JS, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. PloS one. 2021 Jul 12;16(7):e0254523–e0254523.

28. Shoucri SM, Purpura L, DeLaurentis C, Adan MA, Theodore DA, Irace AL, et al. Characterising the long-term clinical outcomes of 1190 hospitalised patients with COVID-19 in New York City: a retrospective case series. BMJ open. 2021 Jun 2;11(6):e049488–e049488.
29. Biadsee A, Dagan O, Ormianer Z, Kassem F, Masarwa S, Biadsee A. Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients. American journal of otolaryngology. 2021;42(4):103065.
30. Wu Q, Zhong L, Li H, Guo J, Li Y, Hou X, et al. A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019. Canadian respiratory journal. 2021 Feb 13;2021:6692409.
31. Shang YF, Liu T, Yu JN, Xu XR, Zahid KR, Wei YC, et al. Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. Journal of internal medicine. 2021 Aug;290(2):444–50.
32. Blomberg B, Mohn KG-I, Brokstad KA, Zhou F, Linchausen DW, Hansen B-A, et al. Long COVID in a prospective cohort of home-isolated patients. Nature medicine. 2021 Sep;27(9):1607–13.
33. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. The Lancet regional health Europe. 2021 Sep;8:100186.
34. Yin X, Xi X, Min X, Feng Z, Li B, Cai W, et al. Long-term chest CT follow-up in COVID-19 Survivors: 102-361 days after onset. Annals of translational medicine. 2021 Aug;9(15):1231.
35. Darcis G, Bouquegneau A, Maes N, Thys M, Henket M, Labye F, et al. Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: a monocentric prospective observational cohort study. International journal of infectious diseases. 2021 Aug;109:209–16.
36. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. The Lancet regional health Europe. 2021 Jul;6:100122.
37. Riestra-Ayora J, Yanes-Diaz J, Esteban-Sanchez J, Vaduva C, Molina-Quiros C, Larran-Jimenez A, et al. Long-term follow-up of olfactory and gustatory dysfunction in COVID-19: 6 months case-control study of health workers. European archives of oto-rhino-laryngology. 2021 Dec;278(12):4831–7.
38. Aranda J, Oriol I, Martín M, Feria L, Vázquez N, Rhyman N, et al. Long-term impact of COVID-19 associated acute respiratory distress syndrome. The Journal of infection. 2021 Nov;83(5):581–8.
39. Caruso D, Guido G, Zerunian M, Polidori T, Lucertini E, Pucciarelli F, et al. Post-Acute Sequelae of COVID-19 Pneumonia: Six-month Chest CT Follow-up. Radiology. 2021 Nov;301(2):E396–405.
40. Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. Journal of neurovirology. 2021 Feb;27(1):154–9.

Journal Pre-proof

41. Frontera JA, Yang D, Lewis A, Patel P, Medicherla C, Arena V, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. Journal of the neurological sciences. 2021 Jul 15;426:117486.
42. Kim Y, Kim S-W, Chang H-H, Kwon KT, Bae S, Hwang S. Significance and Associated Factors of Long-Term Sequelae in Patients after Acute COVID-19 Infection in Korea. Infection & chemotherapy. 2021 Sep;53(3):463–76.
43. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology. 2021 Apr;299(1):E177–86.
44. Taboada M, Moreno E, Cariñena A, Rey T, Pita-Romero R, Leal S, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. British journal of anaesthesia. 2021 Mar;126(3):e110–3.
45. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220–32.
46. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Rodríuez-Jiménez J, Palacios-Ceña M, Velasco-Arribas M, et al. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: A multicenter study. The Journal of infection. 2021 Aug;83(2):237–79.
47. Nguyen NN, Hoang VT, Lagier J-C, Raoult D, Gautret P. Long-term persistence of olfactory and gustatory disorders in COVID-19 patients. Clinical microbiology and infection. 2021 Jun;27(6):931–2.
48. Lindahl A, Aro M, Reijula J, Mäkelä MJ, Ollgren J, Puolanne M, et al. Women report more symptoms and impaired quality of life: a survey of Finnish COVID-19 survivors. Infectious Diseases. 2021 Aug 19;1–10.
49. Qin W, Chen S, Zhang Y, Dong F, Zhang Z, Hu B, et al. Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up. The European respiratory journal. 2021 Jul 22;58(1):2003677.
50. Schandl A, Hedman A, Lyngå P, Fathi Tachinabad S, Svefors J, Roël M, et al. Long-term consequences in critically ill COVID-19 patients: A prospective cohort study. Acta anaesthesiologica Scandinavica. 2021 Oct;65(9):1285–92.
51. Mei Q, Wang F, Yang Y, Hu G, Guo S, Zhang Q, et al. Health Issues and Immunological Assessment Related to Wuhan's COVID-19 Survivors: A Multicenter Follow-Up Study. Frontiers in medicine. 2021 May 7;8:617689.
52. Froidure A, Mahsouli A, Liistro G, de Greef J, Belkhir L, Gérard L, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respiratory medicine. 2021 May;181:106383.
53. González J, Benítez ID, Carmona P, Santisteve S, Monge A, Moncusí-Moix A, et al. Pulmonary Function and Radiologic Features in Survivors of Critical COVID-19: A 3-Month Prospective Cohort. Chest. 2021 Jul;160(1):187–98.

Journal Pre-proof

54. Qu G, Zhen Q, Wang W, Fan S, Wu Q, Zhang C, et al. Health-related quality of life of COVID-19 patients after discharge: A multicenter follow-up study. Journal of clinical nursing. 2021 Jun;30(11–12):1742–50.
55. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and Determinants of Fatigue after COVID-19 in Non-Hospitalized Subjects: A Population-Based Study. International journal of environmental research and public health. 2021 Feb 19;18(4):2030.
56. Parry AH, Wani AH, Shah NN, Jehangir M. Medium-term chest computed tomography (CT) follow-up of COVID-19 pneumonia patients after recovery to assess the rate of resolution and determine the potential predictors of persistent lung changes. The Egyptian Journal of Radiology and Nuclear Medicine. 2021;52(1):55.
57. Mumoli N, Bonaventura A, Colombo A, Vecchié A, Cei M, Vitale J, et al. Lung Function and Symptoms in Post-COVID-19 Patients: A Single-Center Experience. Mayo Clinic proceedings Innovations, quality & outcomes. 2021 Oct;5(5):907–15.
58. Parente-Arias P, Barreira-Fernandez P, Quintana-Sanjuas A, Patiño-Castiñeira B. Recovery rate and factors associated with smell and taste disruption in patients with coronavirus disease 2019. American journal of otolaryngology. 2021;42(5):102648.
59. Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, de Palma G. Neurological and cognitive sequelae of Covid-19: a four month follow-up. Journal of neurology. 2021 Dec;268(12):4422–8.
60. Suárez-Robles M, Iguaran-Bermúdez MDR, García-Klepizg JL, Lorenzo-Villalba N, Méndez-Bailón M. Ninety days post-hospitalization evaluation of residual COVID-19 symptoms through a phone call check list. The Pan African medical journal. 2020 Dec 1;37:289.
61. Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic. Clinical infectious diseases. 2021 Aug 2;73(3):e826–9.
62. Søraas A, Kalleberg KT, Dahl JA, Søraas CL, Myklebust TÅ, Axelsen E, et al. Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. PloS one. 2021 Aug 26;16(8):e0256142–e0256142.
63. Noel-Savina E, Viatgé T, Faviez G, Lepage B, Mhanna LT, Pontier S, et al. Severe SARS-CoV-2 pneumonia: Clinical, functional and imaging outcomes at 4 months. Respiratory medicine and research. 2021 Nov;80:100822.
64. González-Hermosillo JA, Martínez-López JP, Carrillo-Lampón SA, Ruiz-Ojeda D, Herrera-Ramírez S, Amezcua-Guerra LM, et al. Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. Brain sciences. 2021 Jun 8;11(6):760.
65. Skala M, Svoboda M, Kopecky M, Kocova E, Hyrsl M, Homolac M, et al. Heterogeneity of post-COVID impairment: interim analysis of a prospective study from Czechia. Virology journal. 2021 Apr 12;18(1):73.

66. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. Clinical infectious diseases. 2021 Jul 5;ciab611.
67. Wallis TJM, Heiden E, Horno J, Welham B, Burke H, Freeman A, et al. Risk factors for persistent abnormality on chest radiographs at 12-weeks post hospitalisation with PCR confirmed COVID-19. Respiratory research. 2021 May 21;22(1):157.
68. P S, Madhavan S, Pandurangan V. Prevalence, Pattern and Functional Outcome of Post COVID-19 Syndrome in Older Adults. Cureus. 2021 Aug 15;13(8):e17189–e17189.
69. Motiejunaite J, Balagny P, Arnoult F, Mangin L, Bancal C, Vidal-Petiot E, et al. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. The European respiratory journal. 2021 Aug 26;58(2):2101578.
70. Munker D, Veit T, Barton J, Mertsch P, Mümmler C, Osterman A, et al. Pulmonary function impairment of asymptomatic and persistently symptomatic patients 4 months after COVID-19 according to disease severity. Infection. 2021 Jul 28;1–12.
71. Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. Journal of Korean medical science. 2020 Dec 7;35(47):e418–e418.
72. Boari GEM, Bonetti S, Braglia-Orlandini F, Chiarini G, Faustini C, Bianco G, et al. Short-Term Consequences of SARS-CoV-2-Related Pneumonia: A Follow Up Study. High blood pressure & cardiovascular prevention. 2021 Jul;28(4):373–81.
73. Wong AW, Shah AS, Johnston JC, Carlsten C, Ryerson CJ. Patient-reported outcome measures after COVID-19: a prospective cohort study. The European respiratory journal. 2020 Nov 26;56(5):2003276.
74. Garrigues E, Janvier P, Kherabi Y, le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. The Journal of infection. 2020 Dec;81(6):e4–6.
75. Lu Y, Li X, Geng D, Mei N, Wu P-Y, Huang C-C, et al. Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study. EClinicalMedicine. 2020 Aug;25:100484.
76. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emergency radiology. 2020 Dec;27(6):711–9.
77. Fortini A, Torrigiani A, Sbaragli S, lo Forte A, Crociani A, Cecchini P, et al. COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge. Infection. 2021 Oct;49(5):1007–15.
78. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. The European respiratory journal. 2021 Apr 29;57(4):2003481.
79. Tawfik HM, Shaaban HM, Tawfik AM. Post-covid-19 syndrome in egyptian healthcare staff: Highlighting the carers sufferings. Electronic Journal of General Medicine. 2021;18(3).

80. Tleyjeh IM, Saddik B, AlSwaidan N, AlAnazi A, Ramakrishnan RK, Alhazmi D, et al. Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: A cohort study with 4 months median follow-up. PloS one. 2021 Dec 7;16(12):e0260568–e0260568.
81. Stewart S, Newson L, Briggs TA, Grammatopoulos D, Young L, Gill P. Long COVID risk - a signal to address sex hormones and women's health. The Lancet regional health Europe. 2021 Dec;11:100242.
82. Lerner AM, Robinson DA, Yang L, Williams CF, Newman LM, Breen JJ, et al. Toward Understanding COVID-19 Recovery: National Institutes of Health Workshop on Postacute COVID-19. Annals of internal medicine. 2021 Jul;174(7):999–1003.
83. Rajan S, Khunti K, Alwan N, Steves C, Greenhalgh T, Macdermott N, et al. In the wake of the pandemic Preparing for Long COVID. World Health Organization. 2021; Available from: http://www.euro.who.int/en/about-us/partners/
84. Steinman MA, Auerbach AD. Managing chronic disease in hospitalized patients. JAMA internal medicine. 2013 Nov 11;173(20):1857–8.
85. Fofana NK, Latif F, Sarfraz S, Bilal, Bashir MF, Komal B. Fear and agony of the pandemic leading to stress and mental illness: An emerging crisis in the novel coronavirus (COVID-19) outbreak. Psychiatry research. 2020 Sep;291:113230.
86. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594(7862):259–64.
87. Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ (Clinical research ed). 2021 May 19;373:n1098–n1098.
88. Korompoki E, Gavriatopoulou M, Hicklen RS, Ntanasis-Stathopoulos I, Kastritis E, Fotiou D, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. The Journal of infection. 2021 Jul;83(1):1–16.
89. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. Clinical and experimental medicine. 2020 Nov;20(4):493–506.
90. Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet. 2020 Mar 21;395(10228):e52–e52.
91. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Frontiers in immunology. 2021 Jun 30;12:686029.
92. Hayes LD, Ingram J, Sculthorpe NF. More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review. Frontiers in Medicine. 2021;8:2028.
93. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. JAMA Network Open. 2021 Oct 13;4(10):e2128568–e2128568.

94. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA network open. 2021 May 3;4(5):e2111417–e2111417.
95. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Scientific Reports. 2021;11(1):16144.
96. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. BMJ Global Health. 2021 Sep 1;6(9):e005427.
97. Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine. 2021 Jun 1;36.
98. Imrey PB. Limitations of Meta-analyses of Studies With High Heterogeneity. JAMA Network Open. 2020 Jan 10;3(1):e1919325–e1919325.
99. Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. Nature Medicine. 2021;27(7):1129–30.

Journal Pre-proof

Journal Pre-proof

Table 1. Summary of all included studies in descending order by sample size.

Study	Study Design	Location	Sample size	Day zero	Follow-up in days	Assessment Method	Severity
Taquet et al.	Nationwide	USA	236379	Diagnosis date	180	EMR	Mixed IP/OP/ICU
Mei et al.	Multicenter	China	3677	Hospital discharge	144	In person	IP
César Fernández-de-las-Peñaset al.	Multicenter	Spain	1950	Hospital discharge	340	Telephone	Mixed IP/ICU
Chaolin Huang et al.	Single center	China	1733	Hospital discharge	186	In-person	Mixed IP/ICU
Huang et al.	Single center	China	1276	Symptom onset	185, 349	In-person	Mixed IP/ICU
Fernández-de-las-Peñas et al.	Multicenter	Spain	1142	Hospital discharge	213	Telephone, EMR	Mixed IP/ICU
Kim et al.	Single center	South Korea	822	Symptom onset or diagnosis date	195	Online	Mixed IP/OP/ICU
Shang et al.	Multicenter	China	796	Hospital discharge	180	Telephone	Mixed IP/ICU
Søraas et al.	Multicenter	Norway	676	Diagnosis date	132	Online	OP
Qin et al.	Single center	China	647	Hospital discharge	90	In person	IP
Maestre-Muñiz et al.	Single center	Spain	543	Hospital discharge	365	In person	Mixed OP/IP
Qu et al.	Multicenter	China	540	Hospital discharge	90	Telephone, Online	IP
Knut Stavem et al.	Multicenter	Norway	458	Symptom onset	117.5	Online, Postal/Mail	OP
Menges et al.	Nationwide	Switzerland	431	Diagnosis date	220	Online	Mixed IP/OP/ICU
Shoucri et al.	Single center	USA	364	Diagnosis date	158	In-person, telephone	Mixed IP/OP/ICU

Zayet et al.	Single center	France	354	Diagnosis date	289.1	Telephone, online	Mixed IP/OP/ICU
Augustin et al.	Single center	Germany	353	Symptom onset	207	In person	Mixed IP/ICU
Yin et al.	Single center	China	337	Symptom onset	203.4	In person	Mixed IP/ICU
Sigfrid et al.	Multicenter	United Kingdom	327	Hospital discharge	222	Telephone, In person, Postal	Mixed IP/ICU
Boscolo-Rizzo et al.	Multicenter	Italy	304	Symptom onset	365	Telephone	OP
DM Lombrado et al.	Single center	Italy	303	Diagnosis date	371	Telephone, EMR	Mixed IP/OP/ICU
Sathyamurthy P et al.	Single center	India	279	Hospital discharge	90	Telephone	Mixed IP/ICU
Blomberg et al.	Single center	Norway	247	Diagnosis date	180	In person	OP
Clavario et al.	Single center	Italy	200	Hospital discharge	180	In-person	IP
Darcis et al.	Single center	Belgium	199	Hospital discharge	94, 180	In person	Mixed IP/ICU
Riestra-Ayora et al.	Single center	Spain	195	Diagnosis date	180	Telephone	Mixed OP/IP
Jennifer A. Frontera t al.	Multicenter	USA	192	Symptom onset	201	Telephone	Mixed IP/ICU
Pablo Parente-Arias et al	Multicenter	Spain	151	Symptom onset	100.5	Telephone, EMR	Mixed OP/IP
Han et al.	Multicenter	China	144	Symptom onset	180	In-person	Mixed IP/ICU
Sonnweber et al.	Multicenter	Austria	135	Symptom onset	103	In-person	Mixed IP/OP/ICU
Froidure et al.	Single center	Belgium	134	Hospital discharge	95	In person	Mixed IP/ICU
Suárez-Robles et al.	Single center	Spain	134	Hospital discharge	90	Telephone	Mixed IP/ICU

Journal Pre-proof

González-Hermosillo et al.	Single center	Mexico	130	Hospital discharge	90, 180	Telephone	Mixed IP/ICU
Nguyen et al.	Single center	France	125	Symptom onset	221.7	Telephone	IP
Garrigues et al.	Single center	France	120	Hospital admission	110.9	Telephone	IP/ICU*
Mattioli et al.	Single center	Italy	120	Diagnosis date	126	In person	Mixed OP/IP
Tawfik et al.	Multicenter	Egypt	120	Diagnosis date	120	In person	Mixed OP/IP
Leila Simani et al.	Single center	Iran	120	Hospital discharge	180	In-person	Mixed IP/ICU
Jacobson et al.	Single center	USA	118	Diagnosis date	119.3	In person	Mixed IP/OP/ICU
Caruso et al.	Single center	Italy	118	Initial CT chest	180	In person	Mixed IP/ICU
Motiejunaite et al.	Single center	France	114	Diagnosis date	90	In-person	Mixed IP/OP/ICU
Schandl et al.	Single center	Sweden	113	ICU discharge	152	In person	ICU
Aranda et al.	Single center	Spain	113	Diagnosis date	240	In person	Mixed IP/ICU
Mechi et al.	Single center	Iraq	112	Diagnosis date	274	In person	OP
Skala et al.	Multicenter	Czech Republic	102	Diagnosis date	90	In-person	Mixed OP/IP
T. J. M. Wallis et al.	Single center	United Kingdom	101	Hospital admission	96	Telephone, in-person	Mixed IP/ICU
Lindahl et al.	Single center	Finland	101	Hospital discharge	180	Online	Mixed IP/ICU
Biadsee et al.	Single center	Israel	97	Diagnosis date	231	Telephone	OP
Seeßle et al.	Single center	Germany	96	Symptom onset	152, 365	In person	Mixed OP/IP

Boari et al.	Single center	Italy	91	Hospital discharge	120	In-person	Mixed IP/ICU
Taboada et al.	Multicenter	Spain	91	ICU discharge	180	In-person	ICU
Mumoli et al.	Single center	Italy	88	Hospital admission	91	In person	IP
Parry et al.	Single center	India	81	Initial CT chest	100.6	EMR	Mixed IP/OP/ICU
Wong et al.	Multicenter	Canada	78	Symptom onset	91	In-person	Mixed IP/ICU
Dieter Munker et al.	Multicenter	Germany	76	Diagnosis date	120	In-person	Mixed IP/OP/ICU
Liang et al.	Single center	China	76	Hospital discharge	90	In-person	Mixed IP/ICU
Noel-Savina et al.	Single center	France	72	Diagnosis date	129	In-person	Mixed IP/ICU
Elkan et al.	Single center	Israel	66	Hospital discharge	270	Online, telephone	IP
Jessica González et al.	Single center	Spain	62	Hospital discharge	90	In-person, EMR	ICU
Yiping Lu et al.	Single center	China	60	Symptom onset	90	In-person	Mixed IP/ICU
Fortini et al.	Single center	Italy	59	Hospital discharge	123	In-person, telephone	IP
Wu et al.	Single center	China	54	Hospital discharge	180	In person	IP
Seyed Mohammad Hossein Tabatabaei et al.	Single center	Iran	52	Initial CT chest	91	EMR	Mixed IP/OP/ICU

IP = inpatient, OP = outpatient, ICU = intensive care unit, EMR = electronic medical records.

*ICU and IP results presented separately

Journal Pre-proof

Journal Pre-proof

Table 2. Summary of studies reporting Long COVID-19 symptom prevalence with a comparator group. mMRC = modified Medical Research Council.

Authors	Study Design (average follow up in days)	COVID-19 group definition	Comparator group definition	Symptom/outcome assessment method	Newcastle-Ottawa Scale (NOS)	Summary of findings
Huang et al.	Ambidirectional cohort (185 days and 349 days).	Patients with laboratory confirmed COVID-19 discharged from Jin Yin-tan Hospital (Wuhan, China). (n = 1164)	Community adults without COVID-19 from two districts of Wuhan city, matched with cases 1:1 by age, sex and comorbidities.* (n=1164)	Interview, physical examination, questionnaires.	7/9	COVID-19 patients had significantly higher prevalence of any of the following symptoms, as well as prevalence for each individual symptom: fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, diarrhea or vomiting, chest pain, sore throat or difficulty swallowing, skin rash, myalgia, headache, cough. COVID-19 patients had significantly higher mMRC dyspnea scores and reported significantly more difficulty with mobility, personal care, pain or discomfort, anxiety or depression and overall Quality of Life.
Taquet et al.	Retrospective cohort (180 days).	Patients with confirmed COVID-19 diagnosis, aged >= 10 years and alive at time of analysis. Data collected using the TriNetX Analytics Network, consisting of anonymized data from 81 million patients, primarily in the USA.	Propensity matched patients from the same database, with COVID-19 cases matched separately with influenza or respiratory tract infection (RTI, including influenza). Matched for age, sex, race, ethnicity and co-morbidities. ** (influenza n =	ICD-10 codes, EMR.	9/9	COVID-19 had significantly higher hazard compared to both the matched influenza cohort and RTI cohort for mood disorder, anxiety disorder, psychotic disorder, substance use disorder and insomnia.

		(matched with influenza cases n = 105579, matched with other respiratory tract infections (RTI) n = 236038)	105579, RTI n = 236038)			
Riestra-Ayora et al.	Prospective cohort† (180 days).	Health workers from a tertiary care hospital with suspected and symptomatic COVID-19, confirmed by PCR.(n = 195)	Health workers from a tertiary care hospital with suspected COVID-19 with negative PCR, matched for sex and age.. (n = 125)	Interview.	5/9	There was no statistically significant difference in the recovery rate from olfactory dysfunction recovery between those with positive PCR for COVID-19 and those with suspected COVID-19 with negative PCR.
Mattioli et al.	Prospective cohort (126 days).	Healthcare workers at University Hospital of Brescia (Italy) with previous confirmed diagnosis of mild-moderate COVID-19. (n = 120)	Healthcare workers from the same hospital not previously affected by COVID-19. (n = 30)	Interview, physical examination, questionnaires.	5/9	COVID-19 cases did not differ significantly from non-COVID controls in terms of neurological or cognitive deficits, but had significantly higher scores for anxiety and depression.
Elkan et al.	Retrospective cohort† (270 days).	Adult patients discharged from Shamir Medical Center (Israel) with confirmed COVID-19. (n = 42)	Age and sex matched patients hospitalized during the same period as COVID-19 patients due to pneumonia or respiratory infection with	Questionnaire.	6/9	Although there are baseline differences in between groups in terms of co-morbidities, COVID-19 cases had significantly lower self-reported "health change" compared to controls.

			negative COVID-19 PCR. (n = 42)			
Søraas et al.	Prospective cohort (132 days).	Adults testing positive for COVID-19 across four laboratories in South-Eastern Norway, excluding participants later hospitalized. (n = 676)	Adults testing negative for COVID-19 across the same sites, excluding participants later hospitalized. (n = 6006)	Questionnaire.	9/9	COVID-19 positive participants were significantly more likely to report a worsening of health compared to one year prior to follow-up when compared to COVID-19 negative participants.***

*Cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes.

**obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance use disorder, ischaemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer, haematological cancer, chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving an immune mechanism.

***Multivariate regression model including age, sex, chronic diseases, smoking, health professional occupation, income level, fitness and time from COVID-19 testing to follow-up.

[†]Study design was derived from manuscript method section and not author description.

Journal Pre-proof

Captions:

Figure 1. PRISMA diagram

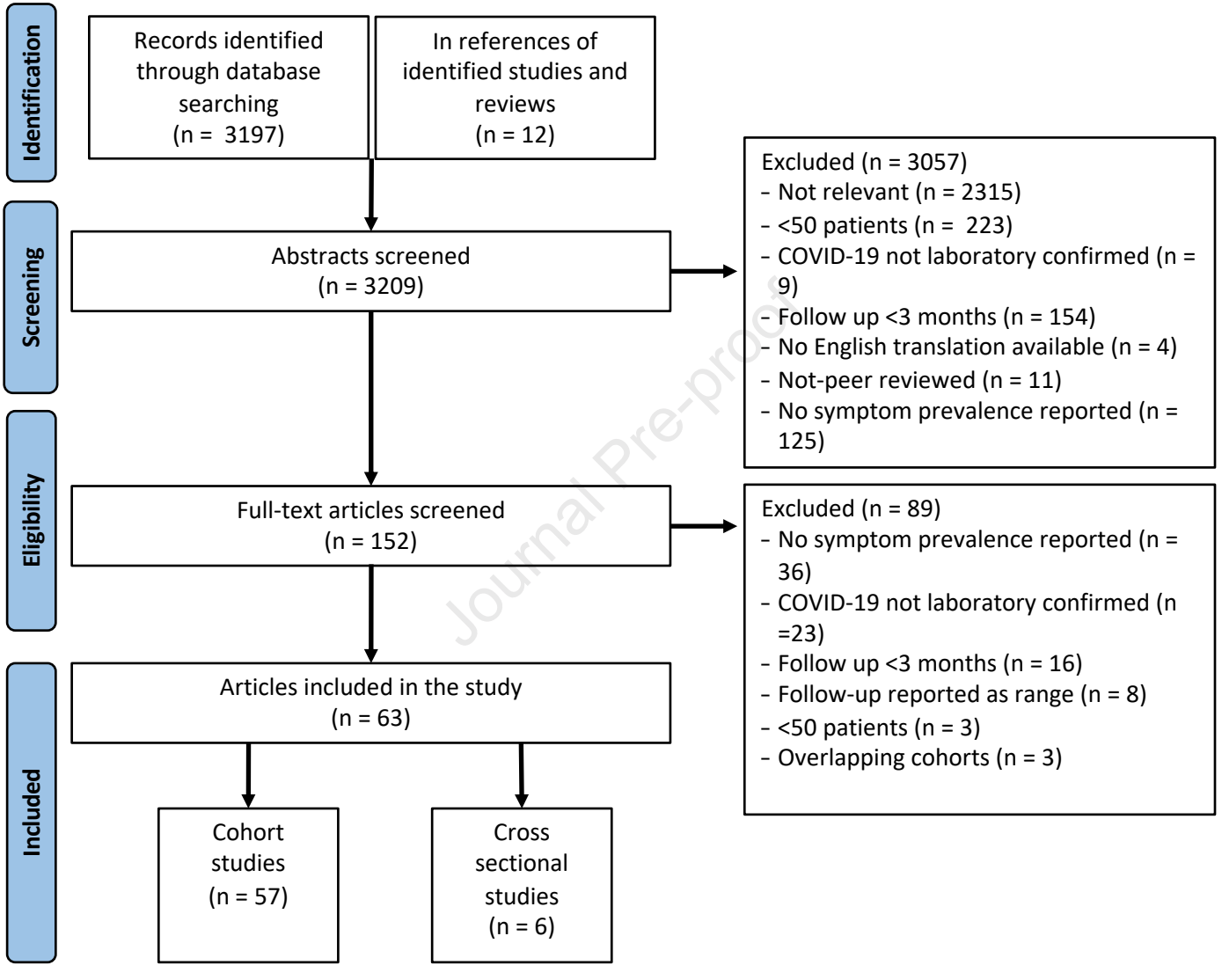
Figure 2. Illustration of meta-analysis results with estimated prevalence of symptoms following acute COVID-19 infection across follow-up intervals of (A) 3-<6 months, (B) 6-<9 months (Number of studies, size of population used to calculate point estimate).

Table 1. Summary of all included studies in descending order by sample size. IP = inpatient, OP = outpatient, ICU = intensive care unit, EMR = electronic medical records.
*ICU and IP results presented separately.

Table 2. Summary of studies reporting Long COVID-19 symptom prevalence with a comparator group. mMRC = modified Medical Research Council.
*Cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes.
**obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance use disorder, ischaemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer, haematological cancer, chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving an immune mechanism.
***Multivariate regression model including age, sex, chronic diseases, smoking, health professional occupation, income level, fitness and time from COVID-19 testing to follow-up.
[†]Study design was derived from manuscript method section and not author description.

Journal Pre-proof

Journal Pre-proof



Journal Pre-proof

Journal Pre-proof

Mental Health

Sleep Disorder	(8; 4369)	24%	95% CI (8-44)	I^2= 98.47%
Depression	(5; 4099)	14%	95% CI (2-33)	I^2 = 98.07%
Anxiety	(7; 4324)	21%	95% CI (6-43)	I^2 = 98.63%

Cardiovascular System

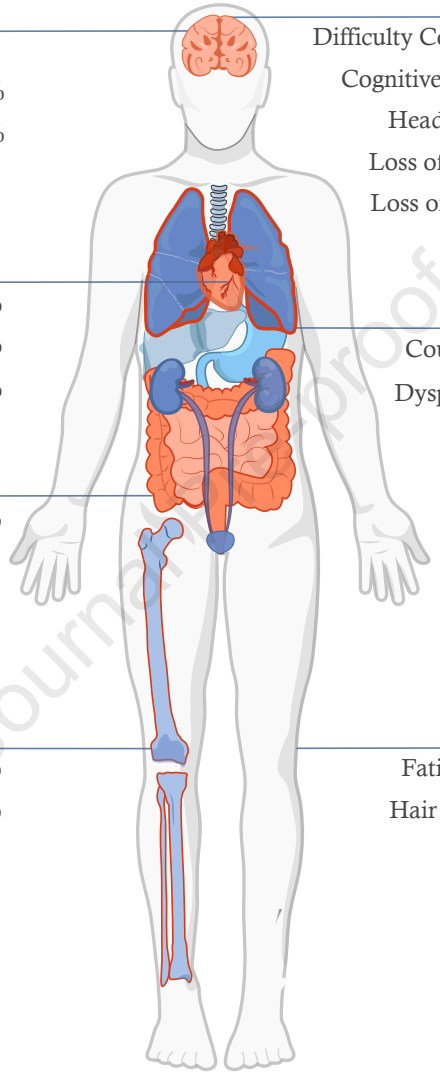
Palpitations	(8; 5401)	14%	95% CI (5-25)	I^2 = 98.43%
Effort Intolerance	(6; 5203)	19%	95% CI (7-35)	I^2 = 99.00%
Chest Pain	(15; 5758)	11%	95%CI (6-16)	I^2 = 95.63%

Gastrointestinal System

Diarrhea	(7; 4908)	10%	95% CI (2-21)	I^2 = 98.36%
Nausea	(3; 480)	8%	95% CI (0-25)	I^2 = N/A

Musculoskeletal System

Joint Pain	(8; 4829)	14%	95% CI (4-27)	I^2 = 98.43%
Myalgia	(10; 5453)	12%	95% CI (4-22)	I^2 = 98.37%



Nervous System

Difficulty Concentrating	(5; 466)	22%	95% CI (15-31)	I^2 = 75.37%
Cognitive Disorder	(6; 670)	14%	95% CI (3-31)	I^2 = 96.37%
Headache	(12; 5699)	12%	95% CI (5-20)	I^2 = 97.88%
Loss of Smell	(16; 5400)	9%	95% CI (4-17)	I^2 = 96.94%
Loss of Taste	(13; 5127)	8%	95% CI (3-15)	I^2 = 96.53%

Respiratory System

Cough	(22; 7539)	15%	95% CI (10-21)	I^2 = 97.44%
Dyspnea	(28; 8132)	25%	95%CI (17-34)	I^2 = 98.34%

Other

Fatigue	(25; 7268)	32%	95% CI (22-44)	I^2 = 98.76%
Hair Loss	(4; 478)	9%	95% CI (2-20)	I^2 = 94.56%

Panel A

Journal Pre-proof

Mental Health

Sleep Disorder	(12; 242000)	29%	95% CI (15-45)	I^2 = 99.71%
Depression	(6; 4377)	23%	95% CI (21-26)	I^2 = 66.33%
Anxiety	(7; 240756)	23%	95% CI (13-33)	I^2 = 99.34%

Cardiovascular System

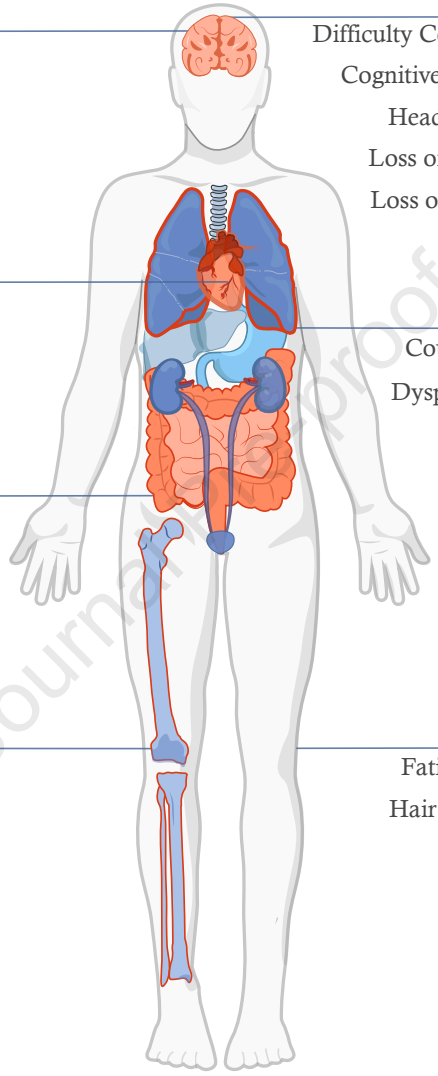
Palpitations	(7; 4735)	14%	95% CI (8-21)	I^2 = 96.92%
Effort Intolerance	(5; 850)	45%	95% CI (25-67)	I^2 = 97.37%
Chest Pain	(10; 4318)	12%	95%CI (8-18)	I^2 = 95.47%

Gastrointestinal System

Diarrhea	(8; 3318)	5%	95% CI (2-11)	I^2 = 96.39%
Nausea	(8; 3419)	4%	95% CI (1-8)	I^2 = 95.18%

Musculoskeletal System

Joint Pain	(8; 5288)	23%	95% CI (15-31)	I^2 = 97.78%
Myalgia	(9; 3490)	19%	95% CI (7-35)	I^2 = 99.05%



Nervous System

Difficulty Concentrating	(4; 854)	22%	95% CI (8-40)	I^2 = 96.89%
Cognitive Disorder	(5; 1987)	15%	95% CI (6-27)	I^2 = 97.56%
Headache	(13; 7170)	14%	95% CI (7-23)	I^2 = 98.97%
Loss of Smell	(17; 6596)	15%	95% CI (10-22)	I^2 = 97.58%
Loss of Taste	(16; 6505)	13%	95% CI (8-18)	I^2 = 96.89%

Respiratory System

Cough	(21; 8737)	12%	95% CI (6-20)	I^2 = 98.01%
Dyspnea	(13; 4384)	25%	95%CI (20-30)	I^2 = 96.78%

Other

Fatigue	(19; 8191)	36%	95% CI (27-46)	I^2 = 98.79%
Hair Loss	(5; 4276)	10%	95% CI (2-22)	I^2 = 99.15%

Panel B